REMARKS

Claims 2, 3, 6, 8-13, 15, 46-48, 50, and 76-99 are pending in this application.

Claims 2, 47, 76, and 87 have been amended herein to clarify that the claimed cell composition comprises about 100% isolated neural cells and neural precursor cells. Support for this amendment is found in the specification at, *inter alia*, page 24, lines 31-38. Claims 2, 8, 47, and 76 have been amended herein to remove the phrase "or combinations thereof" as discussed below.

Claims 13, 84, and 95 have been cancelled herein without prejudice or disclaimer of the subject matter contained therein.

New claims 100-104 have been added herein. Support for these new claims is found, *inter alia*, in the specification at page 22, line 35 to page 23, line 6; page 23, lines 22-24; page 24, lines 11-14; page 26, lines 1-11; page 17, lines 28-31, and in the claims as originally filed. Accordingly, no new matter has been added by these new claims.

Therefore, after entry of these new claims, claims 2-3, 6, 8-12, 15, 46-48, 50, 76-83, 85-94, and 96-104 will be pending in the application.

Applicant thanks Examiner Anne Marie Falk, Ph.D. for her time for participating in a telephonic interview on October 14, 2004 with Ann-Louise Kerner, Ph.D. and Alison Corkery.

Applicant's representatives and the Examiner discussed the outstanding enablement rejections under 35 U.S.C. § 112, first paragraph. Discussed were the enablement rejection related to the phrase "about 100% isolated neural precursor cells" and the clarification that the claimed cell compositions comprise about 100% isolated neural cells and neural precursor cells. Also discussed was the enablement rejection relating to the use of the claimed cell compositions from species other than mice and humans, the enablement rejection related to the genetic modification of human embryonic stem cells, and the enablement of pharmaceutical compositions. Applicant's representatives and the Examiner also discussed the outstanding rejection under 35

U.S.C. § 112, second paragraph as described in more detail herein. This interview is discussed in more detail below where indicated.

The outstanding rejections will be addressed separately below.

1. **Claims 2, 3, 6, 8-13, 15, 46-48, 50, and 76-99 are enabled by the specification as filed under 35 U.S.C. § 112, first paragraph.**

Claims 2, 3, 6, 8-13, 15, 46-48, 50, and 76-99 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicant respectfully traverses this rejection.

a. **The phrase "about 100% isolated neural precursor cells" is enabled.**

Claims 2, 3, 6, 8-13, 15, 46-48, 50, and 76-99 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to provide an enabling disclosure for the claimed cell composition comprising "about 100% isolated neural precursor cells."

Claims 13, 84, and 95 have been cancelled herein without prejudice or disclaimer of the subject matter contained therein. Accordingly, Applicant submits that this rejection is moot with regard to these claims.

In the Office Action dated April 21, 2004, the Examiner acknowledges that Applicant has defined the claimed element, "neural precursor cell" as an immature cell of the nervous system which has the potential to develop into mature nervous system cells such as neurons and glia (astrocytes and oligodendrocytes). (Office Action, page 3 and see specification page 7, lines 15-17). However, the Office Action states that statements in the Declaration of Dr. Bruestle that that the data demonstrate a cell composition of **greater that 99%** neural cells is "quite a different statement from what is being claimed, which is a composition comprising about 100% neural **precursor** cells, not neural cells" and that "differentiated cells do not qualify as neural **precursor** cells, even according to the Applicant's own definition as noted above" (Office Action, page 4).

Claims 2, 47, 76, and 87 have been amended herein to clarify that the claimed cell compositions comprise about 100% isolated neural cells and neural precursor cells as suggested by the Examiner during the interview on October 14, 2004. This fact is evidenced in the specification at, *inter alia*, page 24, lines 31-38, which show data indicating the presence of neural antigens for neural precursor cells as well as neurons, astrocytes, and cells with oligodendroglial morphology in a cell composition according to many of the presently claimed embodiments of the invention.

Additionally, the Declaration of Dr. Bruestle under 37 C.F.R. § 1.132, which was submitted September 5, 2003 as executed (the unexecuted, unrevised version of which was "fully considered" by the Examiner, Advisory Action dated 10/03/2003, page 2) states in part that because there are no unequivocal markers for defining neural precursor cells, Applicant applied "a cocktail of antibodies to markers of both immature (nestin and A2B5) and differentiated (beta-III-tubulin, GFAP, and 04) neural precursor cells" to show that "the cell compositions of the present invention contain more than 99% neural cells" (page 6, paragraph 17).

Furthermore, Figure 5 and the accompanying description on page 12, lines 4-16 of the specification provide data showing that five-day-old neural spheres, derived from CJ7 ES cells, were manipulated to "have disintegrated and differentiated into neural cells." Furthermore, Figure 5D shows "a double immunofluorescence analysis using antibodies to the neuronal antigen beta-III-tubulin (bright signal) and the neural precursor cell marker nestin (dark signal, arrows)" and further, that "**all cells depicted in this field express either of the two markers**" (page 12, lines 11-16) (emphasis added).

Therefore, because all cells expressed either a marker associated with a neural precursor cell or a glial cell (nestin is expressed in astrocytes and microglia, see Declaration, page 6, paragraph 15) or a marker associated with a neuronal cell, Applicant submits that this information in addition to data in the declaration shows that Applicant has indeed demonstrated that the claimed ES cell composition comprises

at or near 100% neural cells or neural precursor cells (otherwise tumors or aberrant cell types would have been detected).

Accordingly, in view of this amendment, it is respectfully requested that this rejection of independent claims 2, 47, 76, and 87 should be reconsidered and withdrawn. Likewise, the rejection of dependent claims 3, 6, 8-12, 15, 46, 48, 50, 77-83, 85-86, and 88-99, which contain all of the limitations of one of claims 2, 47, 76, or 97 should be reconsidered and withdrawn.

b. <u>The specification provides sufficient guidance for one skilled in the art to make and use the claimed cell compositions for species other than mice and humans.</u>

Claims 2, 3, 6, 8-13, 15, 46-48, 50, and 76-99 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to provide an enabling disclosure as "one skilled in the art would have been required to exercise undue experimentation to produce the claimed ES cell-derived neural precursor cell compositions for species other than mice and humans" (Office Action, page 5). Applicant respectfully traverses this rejection.

Claims 13, 84, and 95 have been cancelled herein without prejudice or disclaimer of the subject matter contained therein. Accordingly, Applicant submits that this rejection is moot with regard to these claims.

Applicant submits that not only does the specification provide an enabling disclosure for the preparation of embryonic stem cell-derived neural precursor cells from mice and humans, but the specification states at page 3, lines 8-13 that "pluripotent embryonic stem cells have been isolated from a large variety of species including rat (Iannaconne et al., Dev. Biol. 163:288-292, 1994), hamster (Doetschman et al., Dev. Biol. 127:224-227, 1988), birds (Pain et al., Development 122:2339-2348, 1996), fish (Sun et al., Mol. Mar. Biol. Biotechno. 4:193-199, 1995), swine (Wheeler, Reprod. Fertil. Dev. 6:563-568, 1994), cattle (First et al., Reprod. Fertil. Dev. 6:553-562) and primates (Thomson et al., Proc. Natl. Acad. Sci. USA 92:7844-7848, 1995)." This information is additionally described in the specification at, *inter alia*, page 14, lines 16-

25, which indicates that ES cells can be obtained from other species, including rat, hamster, birds, fish, swine, cattle, primates or embryonic human tissue.

Accordingly, Applicant respectfully submits that the specification is enabled for animals other than mice and humans, and thus, this rejection should be reconsidered and withdrawn.

c. **Rejection relating to genetic modification of human embryonic stem cells.**

The claims also stand rejected as allegedly failing to provide an enabling disclosure "for the genetic modification of human ES cells" (Office Action, page 5). Applicant submits that this rejection is only applicable to claims 13, 84, and 95, which specifically recite that the embryonic stem cells are genetically modified.

Without acquiescing to the propriety of the Examiner's rejection, in order to expedite prosecution of the application, claims 13, 84, and 95 have been cancelled herein without prejudice or disclaimer of the subject matter contained therein. (Applicant notes that due to a typographical error claim 95 did not recite specifically embryonic stem cells. However, as this was the intent, claim 95 is cancelled herein as well.)

However, Applicant notes that this rejection is limited to the "genetic modification of *human* ES cells," not embryonic stem cells from other species. Furthermore, the independent claims are not limited with respect to whether the embryonic stem cells are genetically modified and, therefore, would cover the recited cell compositions (and other related claimed embodiments), including cell compositions derived from embryonic stem cells whether or not the embryonic stem cells are genetically modified. Applicant reserves the right to pursue claims directed to this subject matter in a later case and to argue this rejection in a later case or other appropriate forum.

Accordingly, Applicant respectfully requests that this rejection be reconsidered and withdrawn.

d. The phrase "pharmaceutical composition" is enabled.

Claims 46, 86, 97, and 99 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement for including the phrase "pharmaceutical composition." Applicant traverses this rejection.

First, the Office Action asserts that the claims are directed to compositions for a "therapeutic use" and that the only use contemplated in the specification is for "therapeutic transplantation" (Office Action, page 7). The Office Action further asserts that at least one therapeutic use must be enabled for the claimed compositions. Applicant respectfully disagrees with this rejection.

Applicant provides more than one therapeutic use for the claimed cell compositions. Applicant submits that the present disclosure provides various working examples that utilize well-accepted rodent clinical paradigms (*i.e.* those that physiologically mimic a human disease state) to demonstrate a subsequent and significant biological effect following the transplantation of the presently claimed ES-derived neural spheres.

For example, as illustrated by Figure 8 (see specification, page 13, line 31 to page 14, line 6), neuronal differentiation was visualized following transplantation of the claimed cell composition into the nervous system of ibotenic acid-lesioned rats (a well-accepted animal model for Huntington's disease in humans). Furthermore, three out of four of the lesioned rats receiving the claimed cell composition demonstrated a functional effect – showing a clear reduction of the lesion-induced rotation behavior (described in detail in Example 5.2, page 30, line 27 to page 31, line 11). Subsequent histological analysis indicated the presence of the donor cells in the brain tissue of the recipient animals (page 31, lines 20-21).

Thus, Applicant has successfully demonstrated both a physical and a functional effect following application of the claimed cell composition to ibotenic acid-lesioned rats according to the claimed invention.

Applicant further provides an additional therapeutic use, *i.e.* the transplantation of oligodendroglial /astrocytic precursors into myelin-deficient rats (for the purposes of myelin regeneration necessary for proper neural conduction), which is fully described in Example 4 (beginning on page 26, line 35) and throughout the specification.

Second, the Office Action states that Applicant merely suggests that the compositions can be used to treat a wide variety of diseases without providing "specific guidance as to how the cells can be used for any given disorder," such guidance including "the number of cells to inject, the site of injection..." and further that such therapy techniques are in "their infancy" (Office Action, bottom page 7 to top page 8). Applicant respectfully disagrees.

Applicant submits that the experimental protocols relating to the myelin regeneration (well-known to be vital to neuronal signal transduction) and the ibotenic acid-lesion of the striatum (a well-accepted model for studying Huntington's disease) are fully described above (for example, the precise stereotaxic coordinates for ES implantation are provided for the ibotenic-lesion model, see page 29, beginning with line 19). Together, the present disclosure, in combination with numerous examples from the scientific literature, provide ample support for the use of the presently claimed invention in a variety of biological paradigms.

Also, the Office Action asserts that the present disclosure lacks "applicable working examples directed to therapeutic transplantation." (Office Action, page 9) Applicant respectfully disagrees.

The specification contains detailed examples for myelin repair in a well-known animal model of Pelizeaus-Merzbacher disease (see Example 4, beginning on page 26, line 35) and functional recovery (see Example 5.2, page 30, line 27 to page 31, line 11). With respect to the latter, three out of four of the ibotenic acid-lesioned rats receiving the claimed cell composition demonstrated a functional effect, showing a clear reduction of the lesion-induced rotation behavior. In addition, Example 5 also illustrates that the striatal grafts into ibotenic acid-lesioned animals (an animal model of

Huntington's disease) result in a axonal outgrowth from the graft into the host brain tissue (see Figure 8D described at page 14, lines 5-6), indicating that the neurons derived from the grafted ES cell-derived neural spheres innervate the host brain (page 31, lines 29-37). Thus, Applicant has indeed provided a skilled person with sufficient detail to engage the presently claimed compositions in one or more therapeutic contexts.

In view of the foregoing arguments, Applicant respectfully requests that the oustanding § 112, first paragraph, rejection be reconsidered and withdrawn.

2. Claims 2, 3, 6, 8-13, 15, 46-48, 50, and 76-99 are definite.

Claims 2, 3, 6, 8-13, 15, 46-48, 50, and 76-99 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite in their recitation of "or combinations thereof."

Claims 13, 84, and 95 have been cancelled herein without prejudice or disclaimer of the subject matter contained therein. Accordingly, Applicant submits that this rejection is moot with regard to these claims.

Applicant submits that claim 87 does not recite the phrase "or combinations thereof." Therefore, Applicant submits that this rejection should be reconsidered and withdrawn with respect to claim 87 and claims 88-94 and 96-97 which are dependent thereon.

Claims 2, 8, 47, and 76 have been amended herein to remove the phrase "or combinations thereof." As discussed with the Examiner during the interview on October 14, 2004, the neural precursor cells have the ability to generate mature neural cells, *i.e.*, glial or neuronal cells and the cell compositions of the presently claimed embodiments of the invention may contain neural precursor cells, neuronal cells, glial cells or combinations thereof. However, Applicants acknowledge that one single neural precursor cell according to the presently claimed embodiments of the invention does not differentiate into a combination neuronal/glial cell.

Therefore, Applicant submits that the claims as amended are definite, and accordingly, Applicant respectfully requests that the § 112, second paragraph, rejection be reconsidered and withdrawn.

CONCLUSIONS

In view of the arguments and amendments set forth above, Applicant respectfully requests reconsideration and reexamination of the above-referenced patent application. Applicant submits that the rejections contained in the Office Action mailed on April 21, 2004 have been overcome, and that the claims are in condition for allowance.

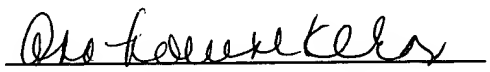
Applicant encloses herewith a Petition for a Three Month Extension of Time pursuant to 37 C.F.R. § 1.136, until October 21, 2004. Please charge our Deposit Account No. 08-0219 the $490.00 fee (small entity) for this purpose.

Applicant also encloses herewith a Supplemental Information Disclosure Statement. Please charge our Deposit Account No. 08-0219 the $180.00 fee for this purpose.

No other fees are believed to be due in connection with this response. However, please charge any underpayments or credit any overpayments to Deposit Account No. 08-0219.

If the Examiner has any questions or amendments that she would like to discuss with the Applicant, she is encouraged to call the undersigned at the number indicated below.

Respectfully submitted,



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Date: October 20, 2004

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